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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/016,850	12/14/2001	Patrick M. Hughes	D-3004	7435

33197 7590 09/29/2005

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EXAMINER	
SPIVACK, PHYLLIS G	
ART UNIT	**PAPER NUMBER**
1614	

DATE MAILED: 09/29/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/016,850	HUGHES ET AL.	
	Examiner	Art Unit	
	Phyllis G. Spivack	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 July 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12 and 14-16* is/are pending in the application.

4a) Of the above claim(s) *7 and 10* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6, 8, 9, 11, 12, 14-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Applicants' Reply filed July 13, 2005 is acknowledged. Claims 1-12 and 14-16 remain under consideration. Claims 7 and 10 remain withdrawn from consideration, 37 CFR 1.142(b), as directed to non-elected inventions. The subject matter under consideration remains those topical ophthalmic compositions of claims 1-6, 8, 9, 11, 12 and 14-16 wherein the therapeutic component is a quinoxaline compound of instant claim 8.

In the last Office Action the claims were rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 3-10 and 32-34 of U.S. Patent 6,562,876.

Following the submission and acceptance of a Terminal Disclaimer, this rejection of record is withdrawn.

Claims 1-6, 8, 9, 11, 12, 15 and 16 were rejected in the last Office Action under 35 U.S.C. 103 as being unpatentable over both Desantis, L., US 2001/0047012, and Collins et al., WO 01/92288. Desantis teaches combination therapy for treating glaucoma comprising administering a glutamate antagonist and an intraocular pressure-lowering compound. Brimonidine, 5-bromo-N-(4,5-dihydro-1H-imidazole-2-yl)-6-quinoxaline, a compound of instant claim 8, is a preferred intraocular pressure (IOP)-lowering compound and memantine is a well established glutamate antagonist. Collins teaches various pharmaceutical conjugates comprising a bioactive antibiotic agent that is covalently bound directly or indirectly to a linker. See page 7, lines 3-16, page 37, line 14, and page 140, lines 9-12, where ophthalmic administration is disclosed. See page 47, lines 9-11, where the conjugate is stated to have a high specificity for sites of

infectious diseases. See page 65, lines 1-6, 19-20, and page 67, lines 1-5, where a discussion of a linker molecule that conjugates one or more agents is given. Amantidine, a compound of instant formula A, is disclosed on page 23, lines 27-28. It was asserted one skilled in the art of formulation chemistry would have been motivated to prepare a pharmaceutical conjugate comprising a therapeutic component covalently linked to an efficacy enhancing component to treat elevated intraocular pressure in view of the combined teachings of Desantis and Collins.

Applicants argue upon topical instillation of the claimed ophthalmic composition, the efficacy-enhancing component (EEC) not only increases the partition coefficient of the therapeutic component (TC), but also *is believed* to bind the retinal epithelium. A reference to the specification on page 11 discloses hypothetical language. "The binding of the EECs to the retinal epithelium *may cause* the TCs to become more bioavailable...".

Applicants further argue the number of glutamate antagonists listed in the Desantis reference is in the thousands and all presently known IOP-lowering agents are encompassed in Desantis.

It is noted the language of the present claims, i.e., efficacy enhancing component and, in particular, therapeutic component, encompass thousands of compounds. Further, the present claims do not exclude antimicrobial therapeutic agents.

Applicants argue no motivation is provided by Desantis to make a conjugate comprising any of the IOP-controlling compounds or glutamate antagonists, or the EEC and TC of the present claims. Applicants note Collins teaches conjugates. However,

Applicants urge no motivation is provided for the combination of amantidines with ophthalmic agents.

Desantis establishes a therapeutic advantage of combining known ophthalmic drugs, such as memantine and brimonidine. Collins teaches pharmaceutical conjugates - with ophthalmic applications – having low molecular weight linkers to which a bioactive agent is covalently bound. Motivation to combine references flows from Collins' teaching that the dosage form, i.e., the conjugate demonstrates a high specificity for a specific target site.

The rejection of record of claims 1-6, 8, 9, 11, 12, 15 and 16 under 35 U.S.C. 103 as being unpatentable over both Desantis, L., US 2001/0047012, and Collins et al., WO 01/92288, is maintained.

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicants are reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this Final Action is set to expire THREE MONTHS from the mailing date of this Action. In the event a first reply is filed within TWO MONTHS of the mailing date of this Final Action and the Advisory Action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the Advisory Action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the Advisory Action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this Final Action.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Phyllis G. Spivack whose telephone number is 571-272-0585. The Examiner can normally be reached from 10:30 to 7 PM.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Christopher Low, can be reached 571-272-951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Phyllis Spivack

September 26, 2005

Phyllis Spivack

1614

PHYLLIS SPIVACK
PRIMARY EXAMINER